BMC Cardiovascular Disorders

Research article

The association between air travel and deep vein thrombosis: Systematic review & meta-analysis

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Published: 19 May 2004

BMC Cardiovascular Disorders 2004, **4**:7

Received: 05 December 2003
Accepted: 19 May 2004

This article is available from: http://www.biomedcentral.com/1471-2261/4/7

Abstract

Background: Air travel has been linked with the development of deep vein thrombosis (DVT) since the 1950s with a number of plausible explanations put forward for causation. No systematic review of the literature exploring this association has previously been published.

Methods: A comprehensive search was undertaken (Data bases searched were: MEDLINE, EMBASE, Cochrane Library) for studies that estimated both the incidence and the risk of DVT in air travellers relative to non-air travellers.

Results: In total 254 studies were identified but only six incidence studies and four risk studies met inclusion criteria justifying their use in a systematic review. Incidence of symptomatic DVT ranged from (0%) in one study to (0.28%) which was reported in pilots over ten years. The incidence of asymptomatic DVT ranged from (0%) to (10.34%). Pooled odds ratios for the two case control studies examining the risk of DVT following air travel were 1.11 (95% CI: 0.64–1.94). Pooled odds ratios for all models of travel including two studies of prolonged air travel (more than three hours) were 1.70 (95% CI: 0.89–3.22).

Conclusion: We found no definitive evidence that prolonged (more than 3-hours) travel including air travel, increases the risk of DVT. There is evidence to suggest that flights of eight hours or more increase the risk of DVT if additional risk factors exist.

Background

The link between air flight and the development of deep vein thrombosis (DVT) and subsequent pulmonary embolism (PE) – so called 'thromboembolic disease'- was first suggested in 1954 by a report describing DVT in a doctor after a 14-hour flight [1]. Since then there has been a massive increase in the popularity of air travel. More than 1.5 billion people travel each year and the International Civil Association Organisation (ICAO) estimates that this figure will rise to over 2 billion by 2005 [2]. Even a small increased risk of venous thromboembolic events (VTE) associated with air travel will cause a substantial number of VTE. Therefore this topic is a matter of public health concern. Much has been written in the medical and popular press about the link between air travel and the development of deep vein thrombosis (DVT) and pulmonary embolism [3-6]. Not surprisingly this has led to an increase in reports of what has been called "economy class syndrome" [7,8] and consequently travellers have been warned about the thrombosis risk [14].

A number of factors in aircraft cabins have been reported to increase the risk of air travellers developing DVT or PE [9]. These include cramped seating positions, immobility, possible dehydration due to consumption of alcoholic drinks and other diuretics such as tea and coffee, and the low humidity of the aircraft cabin, relative hypoxia and reduced barometric pressure.

DVT was traditionally diagnosed on clinical grounds (calf swelling, tenderness and pain). However, researchers recently using sophisticated techniques have shown that asymptomatic DVTs can be detected. The prevalence of asymptomatic deep vein thrombosis in people not suspected of venous thromboembolism on admission to a medical unit was 5.5% and was 17.8% in people over 80 years old [10]. The need for objective diagnosis of VTE is illustrated by the following: Less than 50% of patients with clinically suspected DVT or PE have the diagnosis confirmed when a routine diagnostic imaging is performed [11,12]. There is limited evidence about the clinical importance of asymptomatic calf vein thrombosis. Similarly, studies into the incidence of pulmonary embolism associated with isolated calf vein thrombosis detected asymptomatic embolism by ventilation-perfusion scanning, and the clinical relevance of these findings is unclear [13].

About 6% to 20% of the total population is thought to have some degree of increased clotting tendency. This indicates that there might be a "natural" underlying incidence of DVT in the general population associated with those factors [3].

There has been no large-scale cohort study, which has examined travellers for the development of VTE. The background incidence of symptomatic DVT in the general population is said to vary between 1:3000 (under the age of 40) and 1:500 (over 80) [3,14]. A recent UK study shows the annual incidence of symptomatic thrombosis presented to a hospital in a stable population of 650,000 is about 1/1000 [15]. Symptomatic DVT is important because it predisposes to pulmonary embolism, which is a significant cause of morbidity and mortality [16].

A review of the literature showed no previous systematic review has examined the evidence for an increase in the incidence of DVT amongst air travellers.

The World Health Organization (WHO) recently announced the launch of a comprehensive research programme to investigate the unsolved issue of travellers' thrombosis [17]. However, the study will not be completed until 2006, subject to funding availability.

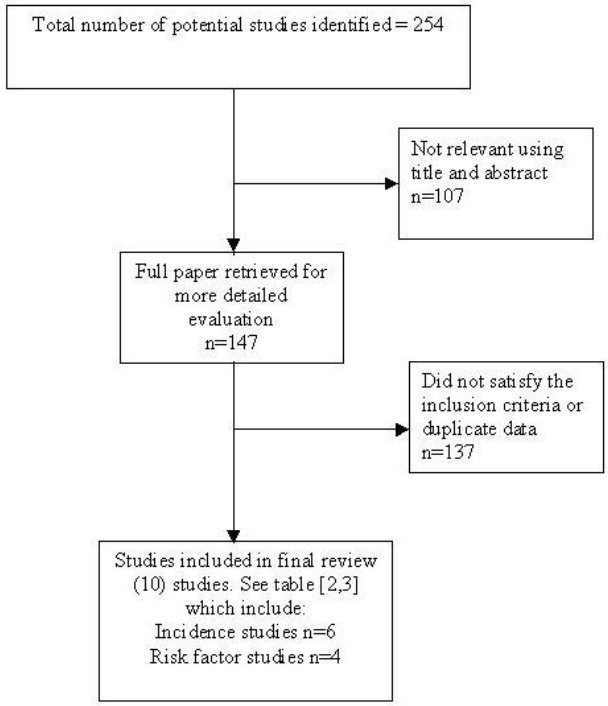

Figure 1
Summary of the included studies

This study reviews the literature to estimate the incidence and the excess risk of DVT in air travellers compared to the non-travelling population.

Methods

Using a combination of text words and MeSH headings, MEDLINE, EMBASE, Cochrane databases (CDSR, CENTRAL) and National Research Register (NRR) were searched using the search strategy shown in Appendix 1 [see Additional file 1]. Citations of included studies and reviews were checked, and experts in the field were contacted. Two types of studies were sought: incidence rate from longitudinal studies and comparative studies to estimate the risk of DVT (i.e. the risk of DVT in air travellers relative to non air travellers). The inclusion criteria are presented in (Table 1).

Two reviewers (YA, RT) independently extracted data from the studies and discrepancies were resolved by discussion. A distinction was made between studies reporting symptomatic DVT and those reporting asymptomatic DVT. Results from the risk studies were pooled using standard

Table 1: Inclusion criteria

Incidence of DVT during air flight	
Design	Any design other than case report
Population	Any individuals who have travelled by air regardless of sex, age or risk status
Exposure	Air travel (short or prolonged flight)
Comparator	Not required
Outcomes	Asymptomatic or symptomatic VTE confirmed by clinical or diagnostic methods, or related mortality
Air flight as a **risk factor** for DVT	
Design	Any comparative study design i.e. randomised controlled trial, prospective or retrospective cohort study or case control study.
Population	Any individuals who have travelled by air regardless of sex, age or risk status.
Exposure	Air travel (short or prolonged flight)
Comparator	No air travel
Outcomes	Asymptomatic or symptomatic VTE confirmed by clinical or diagnostic methods, pulmonary embolus (PE) or related mortality up to month after exposure

meta-analytic methods and expressed as odds ratios. Meta-analysis was carried out using Stata™ 7.0 [18].

Results

254 studies were identified by our searches. Six incidence studies and four risk studies met the inclusion criteria of the review (Figure 1).

Incidence of symptomatic DVT in air travel

Two studies reported the incidence of symptomatic DVT in air travel (Table 2).

Johnson and Evans [19] observed 27 cases of DVT over 10 years in 9,775 pilots, the 10 years incidence was 0.28%. Arfvidsson [20] reported no symptomatic DVTs in 83 individuals, in the 4 weeks following flying (5 hours or more) to and from a medical conference in Hawaii.

Incidence of asymptomatic DVT in air travel

The remaining four studies, Lonflit I (1.4%) [21], Sesarone (4.0%) [22], Lonflit II (4.50%) [21], Scurr (10.34%) [23] reported much higher incidences of DVT following prolonged flights (Table 2). However, in all the remaining four studies, the DVTs reported were asymptomatic conditions, which were detected by using diagnostic methods.

Table 2: Incidence studies

Study Characteristics	**Johnston & Evans (2001)** [19]	**Arfvidsson (2001)** [20]	**Scurr (2001)** [23]	**Cesarone (2002) LONFLIT 3** [22]	**Belcaro (2001) LONFLIT I** [21]	**Belcaro (2001) LONFLIT II** [21]
Population	Healthy workers – pilots	Otherwise healthy- conference attendants	No history of VTE- apparently healthy individuals	High risk group	Both low and high risk	High risk subjects
Definition of VTE	NOT Stated (but it likely to be symptomatic)	DVT symptomatic	DVT asymptomatic	DVT asymptomatic	DVT asymptomatic	DVT asymptomatic
Method of diagnosis	Undefined	Diagnostic test	Diagnostic tests	Diagnostic test	Diagnostic test	Diagnostic test
Nature of exposure	Population of pilots	≥ 5 hours flight	≥ 8 hours flight	Not stated	Average 12.4 hours flight	Average 12.5 hours
Reported rate of VTE n/N	27/9775 (0.28%) during 10 years study	0/83 (0%)	12/116 (10.34%)	4/100 (4.00%)	11/778 (1.41%)	19/422 (4.50%)
Period of follow up	Person-year data is not stated. 10 years study, but little details given about the follow up.	4 weeks	Up to 6 weeks	Not stated Immediately post flight?	24 hours	24 hours

Excess risk of symptomatic DVT in air travellers

Two case control studies examined the excess risk of developing DVT in air travellers relative to non-air travellers (Table 3). Kraaijenhagen [24] identified 788 individuals presenting to an outpatient department with suspected DVT cases of which (186) cases were defined as those who were confirmed by diagnostic tests (compression ultrasonography and D-dimer) and those not confirmed, taken as controls (602). Individuals were questioned about taking a flight of more than 3 hours in the preceding 4 weeks. Using a similar design, Arya et al [25] identified 568 consecutive patients with suspected DVT attending hospital, 185 cases of confirmed DVTs (by duplex ultrasonography) and 383 unconfirmed controls.

Pooling these two studies revealed no evidence of an increase in the risk of DVT with prolonged air travel (odds ratio: 1.11, 95% CI: 0.64 to 1.94) (Figure 2).

Risk of symptomatic DVT in travellers (regardless of travel modes)

Two case control studies reported the excess risk of DVT associated with all forms of prolonged travel (Table 3).

Ferrari [26] assessed 160 patients hospitalised in a cardiology department, presenting with DVT or PE. All journeys (by car, train, sea or air) lasting 4 hours, or more, in the preceding 4 weeks were sought. The same questions were put to an age-matched control group of consecutive patients admitted to the department during the same period, without DVT or PE. Nine (6%) patients with DVT had travelled by air. The odds ratio was not reported for this group.

Samama [27] investigated 494 cases of confirmed DVT reported, and 494 age and sex matched controls (individuals with influenza or rhinopharyngeal syndrome) identified by GPs. Individuals were questioned about long distance travel within the previous 3 weeks.

Table 3: Main study characteristics of the comparative risk of DVT

Study Characteristics	**Ferrari et al (1999)** [26] **France**	**Kraaijenhagen et al (2000)** [24] **The Netherlands**	**Samama (2000)** [27] **France**	**Ayra (2002)** [25] **United Kingdom**
Total sample size	N = 320	N = 788	N = 988	N = 568
Mean age (SD)	66 (16) yrs	61 (17.2) yrs	59.1 yrs (17.3) cases, 58.1 yrs (16.8) in control group	54 yrs
Male (%)	188 (59%)	313 (40%)	454 (36%)	202 (36%)
Sources of cases	Consecutive patients hospitalised for DVT or PE	Consecutive individuals presenting to outpatients with confirmed DVT	Confirmed cases of DVT identified through general practices	Consecutive individuals with confirmed DVT presenting to an A&E Dept or primary care
Sources of control	No DVT or PE age-matched	Individuals where DVT were not confirmed Age & sex matched	No DVT (494) Age/sex matched	Individuals where DVT not confirmed
Case definition	Ultrasound echo-Doppler examination)	Compression ultrasonography, D-dimer assay and clinical follow ups and venography, ventilation perfusion lung scan or angiogram)	Venography, duplex ultrasonography, B mode untrasonography, and /or impedance plethysmography	Duplex ultrasonography
Exposure	Any travel > 4 hrs in last 4 weeks (self report)	Air travel > 3 hrs in last 4 weeks (Patient self report)	Any travel > 6 hrs in last 3 weeks (Patient self report – case notes)	Air travel > 3 hrs* in last 4 weeks (Patient self report)
Comments	Of those cases with DVT only 9 out of 39 patients travel by air. The control group may be less likely to travel by air due to lower social class compared with cases. If control individuals were ill in the last three weeks, they are less likely to have travelled compared with cases.	Many flew less than 5 hours. People included in the study (cases or control) have several potential confounding factor they are not apparently healthy before the travel. There are limited numbers of patients with DVT who travel by air in cases (4) and control, (13). The number of continuous hours that was investigated was more than 3 hours, a period seems shorter than other studies. Participants were asked about travel history before they knew the results of objective diagnosis to avoid referral bias.	Included patients in cases were individuals with surgery and plaster cast in previous 3 weeks flu or rhinopharygeal syndrome matched on sex and age +/- 10 years. Long -distance travel and not specifically air travel that was addressed as risk factor for DVT. The length of travel was not specified. If control individuals were ill in the last three weeks, they are less likely to have travelled compared with cases in the last 3 weeks. The distribution of intrinsic and triggering risk factors are different between case and control patients.	>8 hrs of air travel was not reported as a significant factor. The risk factor in relation to travel is only apparent if there was at least one risk factor

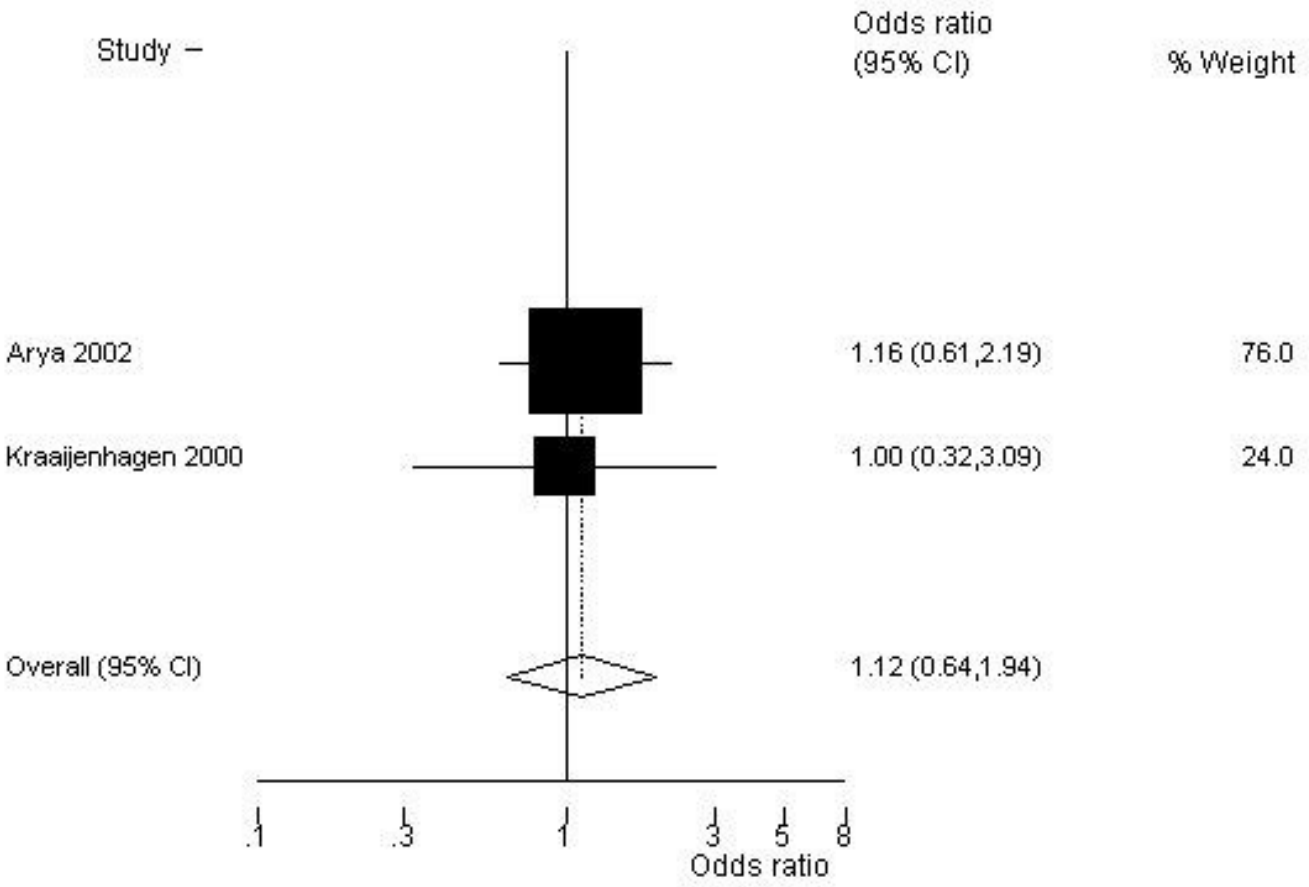

Figure 2
Risk of symptomatic DVT with air travel>3 hours

The pooled results across the four studies revealed evidence of a small but non-statistically significant increase in the risk of symptomatic DVT (odds ratio: 1.70, 95% CI: 0.89 to 3.22) associated with all forms of prolonged travel (Figure 3).

Discussion

We found no evidence to support the claim that air travel (3 hours or more) is associated with an increased risk of developing DVT. We identified a wide range of estimates of the incidence of DVT in air travellers. Symptomatic DVT despite its prominence in the press is remarkably rare. Many published studies related to asymptomatic DVT, the clinical significance of which remains uncertain and needs to be ascertained. Interestingly, there was evidence of a small increase in the risk of symptomatic DVTs associated with all forms of long distance travel. This finding is suggestive that travel by land puts individuals at more risk of DVT than air travel.

With regard to passengers in Kraaijenhagen et al study [24], patients who travel more than 5 hours, no associated risk of DVT was shown. We believe that this finding from the analysis of this subgroup cannot be confidently interpreted. This is because the total number of patients with DVT who travel by plane was reported as 4/186 and in the control (without DVT) 13/602. Any subgroup analysis according to the length of flight e.g. 10 hours would further reduce the number of cases and consequently would reduce the power of the study.

In Arya et al study [25], plane travel >than 8 hours in patients with 568 suspected venous thrombosis was not associated with a statistically increased risk, (OR:1.3, 95% CI :0.6 to 2.8) However this study reported plane travel >8 hours with one or more additional risk factors would significantly increase the risk, (OR: 3.0, 95% CI:1.1 to 8.2).

There are certain factors that make establishing an association rather difficult. These are: the low rate of back-

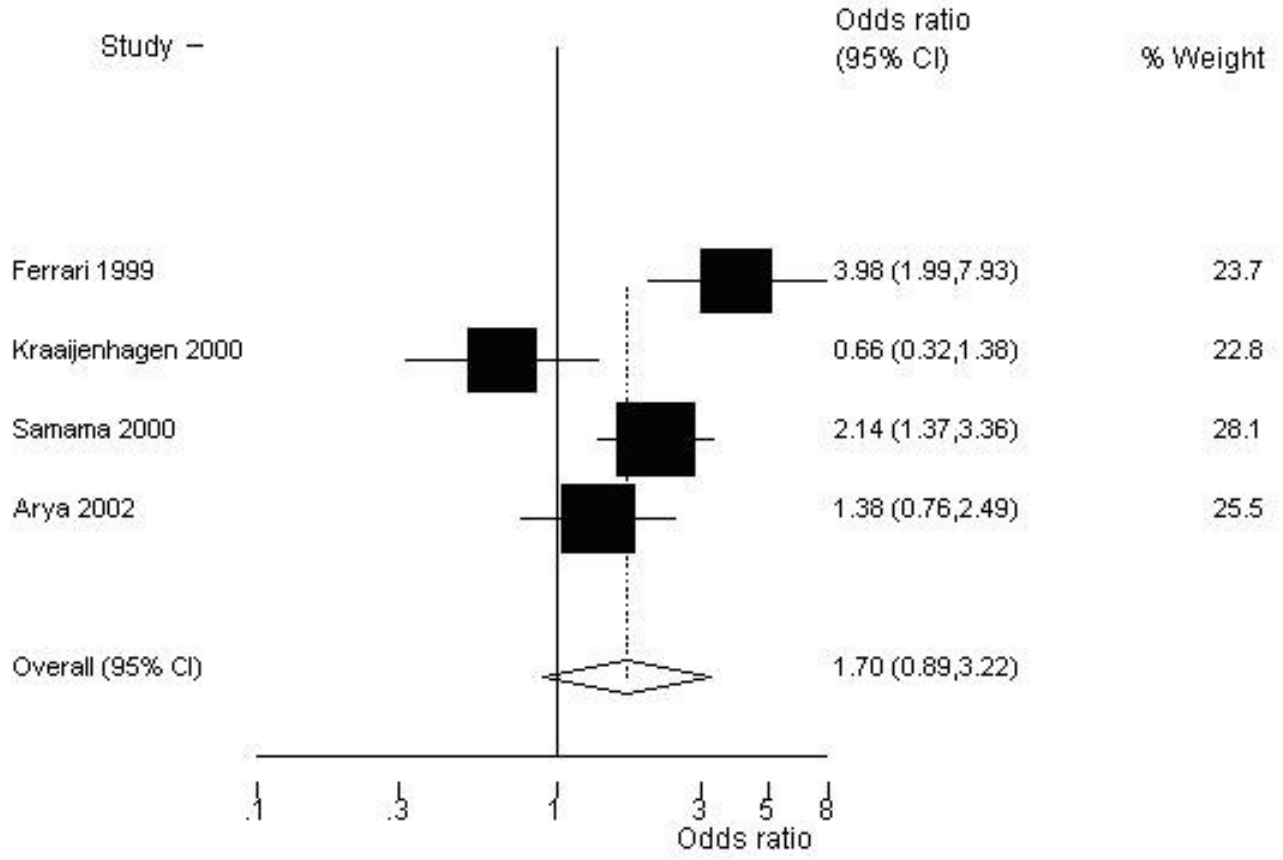

Figure 3
Risk of DVT associated with all modes of travel (i.e. air, care, bus, and rail)

Table 4: The sample size needed to show the risk of DVT in relation to air travel

Background annual incident rate	Background Weekly incidence rate	Assuming Odds Ratio associated with travelling is	Number of air travellers needed/ week	Number of non air travellers/ week	Events of exposed/ week	Events of unexposed / week	Extra events in exposed/ week	Total events/ week
1/1,000	2/100,000	2	1,275,418	1,275,418	52	26	26	78
1/1,000	2/100,000	3	392,463	392,463	24	8	16	32

ground incidence of thrombosis in the population and the low exposure to flying in the individual level and the short duration of exposure.

Given the limited amount of evidence available, this review has insufficient power to confirm a statistically significant increase in risk of DVT associated with air travel, if such a risk exists. It is therefore tempting to suggest that we should await the publication of data before we can establish the relationship between air travel and DVT. The likely estimates of incidence and increased risk are such that the required sample size may be unobtainable. Based on the plausible range of increased risk observed in this review (i.e. odds ratio of 1.10 to 1.94), follow up of about a million air travellers (plus control) would be required to confidently confirm an increased risk. We cannot imagine that such a large study will ever be performed (Table 4). The total number of individuals in this review was n = 1025 with a history of travel and n = 1639 of those without a history of recent travel. Therefore the combined studies are grossly under powered to detect any reasonable increased risk associated with air travel. Table 4 shows

the sample size needed to show the risk of DVT, assuming 80% power and 5% significance. Background weekly incidence was stated to reflect the fact that any added risk from travel would occur within a week of travel. It is assumed also that there is no more than one episode of travel /week (Table 4).

If flight longer than 8 hours were associated with a very high risk of DVT (e.g. Odds ratio 4) sample size studies suggest that 4,400 passengers (plus suitable controls) would be needed. Due to problems with matching, follow up etc, this number should probably be increased up to ten fold (44,000 passengers) [28].

It would be convenient to limit any future case control studies to very long flights, and in people who travel very frequently. The justification for this suggestion is that if such frequent travellers show no increased risk, then it is very unlikely that infrequent air travellers or those who travel only for a short flight would be at an increased risk.

Conclusions

We conclude that there is currently no definitive evidence that air travel increases the risk of DVT. However, there is some evidence to suggest that flights of eight hours or more increase the risk of DVT if additional risk factors exist. Moreover, given the low incidence of DVT in the general population we may never know if air travel increases the risk of DVT because studies with the required sample size to detect a significantly increased risk are unlikely to be sponsored.

Competing interests

None declared.

Authors' contributions

YA and RT conceived the design of the study. SB undertook the searches. YA and RT undertook the data extraction and data analysis. YA, RT, AR involved in the interpretation of the study results. YA drafted this manuscript although all authors provided comments on the draft and have read and approved the final version. YA will act as a guarantor.

Additional material

Additional File 1

The search strategy which was used in this systematic review. A similar search strategy was adapted to search in Embase and Cochrane databases. (last search 31st January 2003)

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Acknowledgements

All funding for this project came from the regional or national (UK) NHS.

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Pre-publication history

The pre-publication history for this paper can be accessed here:

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